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EDITORIAL

Hormone replacement therapy in Turner syndrome is important—a new meta-analysis points at many shortcomings in the available literature

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Turner syndrome (TS) can by most standards be viewed as a rare condition, although it is one of the more common rare conditions. As in all rare conditions, it is difficult to accumulate sufficient data to base treatment and care on evidence and therefore many aspects of TS is based on expert opinion. And since ovarian dysgenesis is almost inevitable early in the lives of most females with TS, estrogen replacement therapy (ERT) is cornerstone to appropriate treatment of TS, to induce puberty and uphold female sex characteristics, maintain bone mass, body composition, and possibly to avoid undue cardiovascular morbidity and positively impact neurocognitive development. However, hard endpoints are not available within the realm of TS research and much has been extrapolated from the literature concerning the effects of ERT in the postmenopausal setting. And such extrapolation may not be valid. Just considering the lengthy discussions concerning the WHI study and the possibility that the timing hypothesis for ERT exists and that the timing of start with ERT may therefore be of great importance [1]. In addition ascertainment bias is a problem in TS research, since less than two-thirds of all TS are ever diagnosed [2], decreasing the validity of clinical studies of TS.

A new meta-analysis and systematic review takes a critical view at effects of ERT on bone and cardiovascular outcome in TS and includes all randomized clinical trials (RCT) on the subject [3]. Not surprisingly, only 9 RCTs could be included in quantitative assessment of effects and furthermore there were pronounced differences in the drugs used, the duration of studies spanning from 2 to 66 months, the age of the TS in the different studies and the route of administration. Therefore a pronounced inconsistency of effects across studies was identified. In addition to RCTs, the meta-analysis also includes cohort studies. Furthermore, only one study reported hard endpoints concerning bone (fractures), while no studies reported cardiovascular related hard endpoints, and thus the meta-analysis reports mainly surrogate endpoints such as change in Bone mineral density (BMD) and high density lipoproteins (HDL). Thus, this meta-analysis highlights the deplorable lack of studies within TS reporting hard endpoints and clearly emphasizes the need for such future studies. Nevertheless, the meta-analysis allows the authors to conclude that cohort studies indicate that ERT improves BMD, with physiological 17β-estradiol seemingly better than synthetic estrogens (such as ethinyl estradiol which is normally used in contraceptive pills). This finding, although data were not of high quality, is interesting, since recommendations have long focused on using physiological supplementation, with many clinicians being uneasy with the use of synthetic compounds for many years in TS [4].

Results from the RCTs concerning cardiovascular surrogate markers show that oral 17β-estradiol is superior to transdermal 17β-estradiol in increasing HDL-cholesterol, while there was no difference in the effect on total cholesterol, LDL-cholesterol and triglycerides. This effect of oral versus transdermal 17β-estradiol has also been noted in RCTs in postmenopausal women.

The data from the original studies included in the meta-analysis were not of sufficient quality to base any

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conclusion as to quality of life during ERT or adverse events in relation to treatment, and thus much larger studies will be needed to answer important questions related to quality of life and adverse events in relation to ERT.

The authors of the meta-analysis prudently notes that we still need "prospective long follow up trials that include assessment of fracture events, BMD values adjusted for height, as current measurements do not correct for bone and body size, a concern in patients with TS who have shorter stature and smaller bones; comparative effectiveness studies of ERT types and routes of administration and earlier ERT interventions given that 90% of women's peak BMD is reached by 18 years of age" [3].

Many of the studies in the current meta-analysis only included few participants, which adds to the low or very low quality of the data, and as also noted by the authors, this calls for much larger studies in the future. Such studies will likely only be possible if international collaborations are undertaken, since most known TS specialized clinics around the world do not care for the number of individuals necessary to conduct very large RCTs. Therefore, I will end this editorial by calling for different centers to join hands in conducting such studies aiming at including more than 1000 TS in either RCTs or cohort follow-up studies. This should certainly be possible within the EU.

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Compliance with ethical standards

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